Immunological risk assessment: The key to individualized immunosuppression after kidney transplantation

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Immunological risk assessment: The key to individualized immunosuppression after kidney transplantation

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A B S T R A C T

The wide range of immunosuppressive therapies and protocols permits tailored planning of the initial regimen according to the immunological risk status of individual patients. Pre-transplant risk assessment can include many factors, but there is no clear consensus on which parameters to take into account, and their relative importance. In general younger patients are known to be at higher risk for acute rejection, compounded by higher rates of non-adherence in adolescents. Donor age and recipient gender do not appear to exert a meaningful effect on risk of rejection *per se*, but black recipient ethnicity remains a well-established risk factor even under modern immunosuppression regimens. Little difference in risk is now observed between deceased- and living-donor recipients. Immunological risk assessment has developed substantially in recent years. Cross-match testing with cytotoxic analysis has long been supplemented by flow cytometry, but development of solid-phase single-bead antigen testing of solubilized human leukocyte antigens (HLA) to detect donor-specific antibodies (DSA) permits a far more nuanced stratification of immunological risk status, including the different classes and intensities of HLA antibodies Class I and/or II, including HLA-DSA. Immunologic risk evaluation is now often based on a combination of these tests, but other assessments are becoming more widely introduced, such as measurement of non-HLA antibodies against angiotensin type 1 (AT1) receptors or T-cell ELISPOT assay of alloantigen-specific donor. Targeted densensitization protocols can improve immunological risk, notably for DSA-positive patients with negative cytotoxicity and flow cross-match. HLA mismatch remains an important and undisputed risk factor for rejection. Delayed graft function also increases the risk of subsequent acute rejection, and the early regimen can be modified in such cases. Overall, there is a shift towards planning the immunosuppressive regimen based on pre-transplant immunology testing although certain conventional risk factors retain their importance.

1. Introduction

The transplant clinician can plan many different immunosuppressive regimens for kidney transplant patients, tailored to each specific need. With the immunosuppressive armamentarium now including various induction therapies, calcineurin inhibitors (CNIs), antiproliferative therapy (mycophenolic acid) and mammalian target of rapamycin (mTOR) inhibitors, and several steroid dosing strategies, individualization according to particular patient profiles has become more possible than ever before.

Unless clear risk factors for drug-specific side effects are present, the key determinant when deciding upon a regimen is the patient's immunological risk status and immunosuppression should be adapted according to the risk for graft rejection [1]. However, although many factors may contribute to a patient's risk status, only the number of human leukocyte antigen (HLA) mismatches has been universally agreed to increase risk [1] and the relative importance of other variables often remains uncertain [2]. Recent clinical trials which have selectively recruited 'high risk' patients have chosen different criteria for entry: only sensitization based on panel reactive antibodies (PRA) have been included consistently and, perhaps surprisingly, HLA mismatch has not been included [3–8]. Additionally, development of single

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antigen testing for donor specific antibodies (DSA) using Luminex® technology has, where available, considerably refined the evaluation of risk.

This article considers the contributions made by recipient, donor and transplant factors toward the immunological risk status of kidney transplant patients at the time of transplant, to assist clinicians when planning the most appropriate immunosuppressive regimen for individual recipients.

2. Impact of graft rejection

The incidence of acute rejection after kidney transplantation has declined substantially since the mid-1990s, stabilizing in recent years to between 10% and 25% by one year post-transplant depending on the level of immunological risk [9,10]. A large US registry analysis based on data from 2004 to 2007 indicates that acute rejection increases the risk of death-censored graft survival by over 70% compared to rejection-free transplants [11]. This, however, masks widely varying effects of different types of acute rejection. The majority of episodes are mild cellular rejections (Banff grade I or IIA) and may have little or no impact on graft outcomes. Two large registry analyses from the mid-2000s [12,13] found that in patients whose graft function recovers after rejection (for example to >85% versus baseline), subsequent graft survival is unaffected. Instead, the effect of cellular rejection on graft survival is largely restricted to more severe episodes without recovery of near-baseline function [12,13] and late acute rejection (after month 3) [14].

An entirely different picture emerges concerning antibody-mediated rejection (AMR), which is highly predictive for kidney graft loss [15–17]. One analysis of biopsies in 56 patients who subsequently progressed to graft failure found that AMR, or mixed AMR/cellular rejection, was present in 75% of cases [15]. Mixed rejection [17] and late AMR (>6 months post-transplant) [18] are both difficult to treat and carry a particularly dismal prognosis, and even subclinical AMR significantly lowers graft survival rates [18].

It would seem that immunosuppressive regimens which carry a slightly higher risk for mild, reversible cellular rejection may be acceptable if they offer other benefits, such as fewer long-term complications. Where immunological risk is deemed to be high, however, this trade-off is likely to be less successful. For patients at increased risk for AMR, the importance of preventing AMR is paramount.

A detailed discussion of early immunosuppression options – and longer-term regimens based on the post-transplant course – is beyond the scope of this article. Key points, however, are summarized in Table 1.

Table 1
Overview of early immunosuppression options after kidney transplantation according to immunological risk status.

	Immunologic risk status	Comments
Induction	Low/moderate risk	IL-2R antagonist [1,24]
	Higher risk[a]	T-cell depleting antibody [1,25,26]
CNI therapy	Low/moderate risk	CNI avoidance generally not advised (possible with belatacept [27,28]) Low-exposure CNI + mTOR inhibitor from time of transplant is feasible [29,30]
	Higher risk[a]	Standard CNI protocol is generally advisable
Steroid avoidance	Low/moderate risk	Early steroid avoidance (<7 days) is a possibility with tacrolimus as CNI [31] and induction is advisable [1]. T-cell depleting antibody may be preferable to IL-2RA induction [32–34]
Desensitization[b]	ABO incompatible living-donor transplants	Rituximab ± IVIG ± plasmapheresis or immunoadsorption [22,23]
	Sensitized patients with DSA	IVIG ± rituximab ± plasmapheresis or immunoadsorption [19–21] ± induction with T-cell depleting antibody

[a] For example, retransplants, prior pregnancy, blood transfusion, HLA-antibody positive.
[b] Usually in living donor transplantation.

3. Impact of recipient and donor demographics

Younger age at the time of transplantation increases the risk for acute rejection [1], an effect attributed partly to age-related changes in the T-cell effector immune response in older patients [35] and partly due to lower adherence to the prescribed regimen (See '*Adherence to medication*' below). An analysis by Tullius et al. of over 100,000 kidney transplant patients registered with the United Network for Organ Sharing (UNOS) registry during 1995 to 2008 found that each successive decade of age above 39 years was associated with a significant reduction in acute rejection during the first year post-transplant (Fig. 1) [36,37]. Another large registry analysis, involving 27,707 patients transplanted in the US during 1995 to 2002, showed that after adjustment for confounding factors, recipients aged 18–44 years were 23% more likely to experience acute rejection by year 1 than those aged 44–59 years [38]. Other registry [39] and large single-center [15,40] analyses have consistently reported younger age to predict risk for acute rejection.

Conversely, there is evidence that a graft from an older donor, presumably with greater immunogenicity, adversely affects risk of rejection [1]. The large UNOS analysis by Tullius and colleagues found that acute rejection rates increased for donors aged older than 29 years (Fig. 1) but the difference was not significant for all age groups [36]. Analyses of other data sets have shown mixed results [40–43] regarding the relative impact of donor age on immunological risk, but overall donor age is likely to play a less important role in risk assessment than recipient age.

A potential influence for recipient gender on immunological risk remains controversial. The largest population to be studied, a series of 27,707 patients from a US registry, found a higher risk of acute rejection in male recipients [38] while non-registry studies have reported either a higher risk in females [39,40] or no difference [15,41]. The lack of consistent data – and a paucity of results from recently transplanted cohorts – does not support inclusion of gender *per se* in an immunological risk assessment so long as females are not sensitized by previous pregnancies (see below).

Black recipient ethnicity is a well-established risk factor for acute rejection after kidney transplantation even under modern immunosuppression regimens [39,42,44]. African Americans have a higher frequency of CYP 3 A5 polymorphism (CYP4503A5*1 genotype), which is associated with low tacrolimus exposure for a given dose [45], contributing to an increased risk for rejection. A prospective, multicenter study of 901 patients given tacrolimus and mycophenolic acid maintenance therapy found the one-year incidence of biopsy-proven acute rejection (BPAR) to be approximately twice as high in African-American versus non-African American patients (14.1% versus 7.5%; hazard ratio [HR] 1.93; 95% CI 1.19–30.09; 0.007) [44]. One recent US registry analysis has suggested that the effect of black ethnicity may be concentrated in younger patients [46]. In an analysis of 112,120 patients transplanted during 2000–2009, Schold et al. observed an increase in rejection risk of 33% for African Americans in the 18–33 age group but no difference compared to other ethnic groups in patients aged over 65 years [46]. Younger black recipients, in particular, appear to require relatively intensive immunosuppression.

Morbidly obese patients (body mass index ≥35 kg/m^2) may be at higher risk for rejection but otherwise weight is not an influencing factor [39]. Similarly, other clinical characteristics, including HIV infection [47], hepatitis C infection [38,48], cause of end-stage renal disease [38], duration of dialysis [15] or the presence of diabetes [15,39] do not significantly affect the risk of rejection.

4. Donor graft characteristics

Historically, deceased-donor grafts have been associated with a higher rate of rejection than those from living donors. Gore et al.

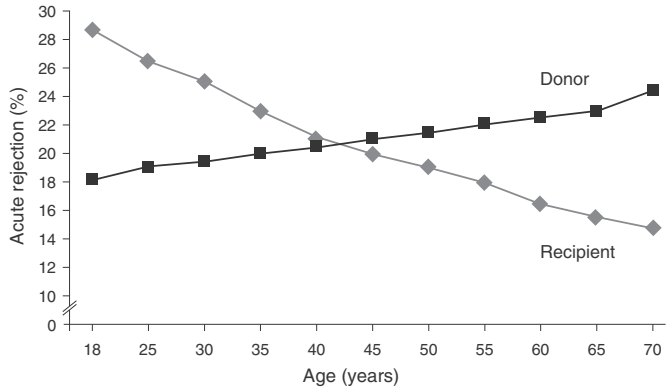

Fig. 1. Association between acute rejection at one year after kidney transplantation and age of the recipient and donor, based on UNOS data from 108,188 patients transplanted during 1995 to 2008. Adapted from reference [37]. Reproduced with permission.

described an analysis of over 27,000 kidney transplants performed during 1997 to 1999, 33% of which were from living donors [39]. Recipients of a living-donor graft were significantly less likely to experience acute rejection. However, the latest data reports from the US [9,49] show only a 1%–2% increase in acute rejection rates for deceased-donor patients, so under contemporary immunosuppressive regimens the type of donor seems less influential. Living-related versus living-unrelated donation does not affect rejection risk [50,51].

Single-center analyses have not suggested any adverse effect of expanded criteria donation on rejection risk versus standard criteria grafts [52,53], although recipients of an expanded criteria graft experience inferior graft survival [54]. Similarly, the cause of donor death (brain death or cardiac death) does not influence risk of rejection [55].

5. Adherence to medication

Non-adherence to the immunosuppressive regimen is, inevitably, a major influence on rejection risk and is estimated to occur in a fifth of kidney transplant recipients [56]. In some cases, a high risk of non-adherence may be identifiable pre-transplant, warranting modifications to the immunosuppressive regimen. Increasing recipient age positively correlates with adherence [57,58]. In an analysis by Greenstein et al., recipients aged less than 25 years were approximately 50% more likely to be poorly adherent than older patients [57]. Adolescents are particularly prone to poor adherence. A recent systematic review of 36 publications found that the prevalence of non-adherence was 32% higher in adolescents than in younger patients, and that almost one in four late acute rejection episodes was associated with non-adherence [59]. Other pre-transplant clues to an increased risk for non- adherence include poor attendance at dialysis sessions and, although less easy to define, attitudes to pre-transplant medication taking, access to the pharmacy and drug funding and social support [60–62].

6. Laboratory assessment of immunological risk

Historically, immunological risk was assessed solely on the basis of T-cell or B-cell cross-matches and complement-dependent cytotoxic (CDC) HLA antibody testing. A positive CDC cross-match has been known for several decades to dramatically increase the host immunological response, with unacceptable rates of graft loss [63]. B-cell cross-match, even with negative T-cell cross-match, is also highly unfavorable [64]. Increasingly, however, it has been recognized that following the first T-cell mediated response, B-cell activation and differentiation lead to plasma cell production and generation of antibodies which represent a late component of the immune cascade. Cross-match testing still includes cytotoxic analysis, but for many years has been supplemented by flow cytometry or ELISA assays to measure anti-donor antibodies. The increased risk for rejection in the presence of HLA class I or II is well-established, regardless of donor specificity. However, a major further step forward has been the development of solid-phase single-bead antigen testing of solubilized HLA (Luminex®) to detect HLA donor antigen specificities providing a far more nuanced interpretation of immunological risk. Currently, immunologic risk is typically based on a combination of results. For example, a patient could be considered at intermediate risk if PRA was >5% and HLA antibodies against specific HLA antigens were present, independent of whether DSA could be determined, after a previous immunization event such as pregnancy, blood transfusion or previous transplant [65]. A patient with negative CDC, 200–250 mcs on flow cytometry and DSA >3000 mean fluorescence intensity (MFI) would be regarded as intermediate risk. A patient with high PRA (e.g. >25%), or specific HLA antibodies after an early previous transplant lost due to immunological causes would be regarded as high risk and could be a candidate for HLA-DSA desensitization.

New approaches are being developed which may help to further refine pre-transplant risk stratification. These variously address the potential contribution of different classes and intensities of HLA-DSA, complement (C1q)-fixing HLA-DSA, HLA non-DSA and non-HLA antibodies, and their interactions. Several recent findings can already be taken into account when evaluating risk. The presence of both preformed DSA class I and class II at the time of transplant is associated with a particularly high rate of graft loss [66]. Antibodies against non-HLA targets have also emerged as a potentially important marker of risk. Non-HLA antibodies against angiotensin type 1 (AT1) receptors prior to transplant have been shown to increase the risk for humoral rejection [67,68] and irreversible graft injury [69]. Not all types of antibody are relevant to planning of the immunosuppression regimen, however. Development of complement-fixing DSA after transplantation is associated with a particularly high risk for AMR and graft loss [70], for instance, but occurs only rarely prior to transplantation [66].

New assays can also estimate cell-specific responses to engraftment. One widely-tested modality is the T-cell ELISPOT assay, which measures alloantigen-specific donor responsiveness as an estimate of immunological risk. Large validation studies from the US [71,72] and Europe [73] have shown that a negative ELISPOT result indicates a 'low response' patient in whom tolerogenic protocols could be pursued, although the test is time-consuming and requires large volumes of blood so may be best suited for living-donor recipients. Combined use of several techniques, including more recent tests, permits accurate assessment of risk. A minority of patients (e.g. 30%) who are negative for HLA-antibodies and for HLA-DSA, for AT1 receptor antibodies, and for a response on the ELISPOT assay can confidently be regarded as low risk, and immunosuppression tailored accordingly. Patients who are negative for, or have a low level of, HLA antibodies overall, non-cytotoxic HLA antibodies or even HLA-DSA, with a low or moderate positive result for anti-AT1 receptor antibodies but who have a positive

ELISPOT test are at intermediate risk. Those with HLA DSA and who are highly positive for AT1 receptor antibody and ELISPOT tests are at high risk for AMR; those with low or intermediate DSA may be candidates for desensitization protocols [68,74,75].

Pre-transplant serum concentrations of the soluble CD30 molecule, a member of the tumor necrosis factor receptor superfamily, have also shown promise as predictive markers for tubulitis in the graft [76], but data are mixed concerning predictive value for AMR [76,77].

7. Sensitization after pregnancy

In a single-center study of 301 female kidney transplant patients with at least one previous pregnancy, levels of HLA antibodies at each HLA locus increased with the number of live births [78]. A smaller single-center study, of 64 transplants with pre-formed DSA, found that 32% of the detected HLA specificities were induced by pregnancy, and that the increase from pre-transplant DSA levels to the peak level by day 30 post-transplant was higher for pregnancy-induced specificities than for those induced by prior transfusion or transplantation [79]. Female patients with one, or particularly more than one, prior pregnancy should be considered to be at least intermediate immunological risk even if DSA level is low at time of transplant.

8. Immunologic risk after desensitization

Desensitization protocols are now used in more than half of US transplant centers for sensitized living-donor kidney transplant candidates [80]. Since desensitization is usually impractical in deceased-donor transplants, the acceptable mismatch program successfully practiced in the Eurotransplant allocation area represents a feasible alternative approach. However, there is still no consensus regarding which patients should receive desensitization, or the optimal combination, dose or timing of protocols [19,81]. Establishing the immunological risk of a patient after desensitization treatment is challenging not only because of this heterogeneity of approaches, but also because of the relatively low numbers of patients to analyze. Orandi et al. analyzed rates of graft loss in the largest cohort of desensitized living-donor recipients so far, based on 1025 patients registered with United States Renal Data System (USRDS) [82]. Graft loss after desensitization was far higher in patients with positive cytotoxic cross-match than in those with positive flow cross-match (but negative cytotoxic cross-match). Patients who tested positive on Luminex® but were negative for cytotoxic or flow cross-match showed only a slight increase in risk compared to compatible transplants [82]. In a single-center analysis, Gloor et al. demonstrated that patients with cytotoxic cross-match have a high rate of AMR (~50%) despite desensitization (Fig. 2) [83]. Even after intensive desensitization using plasmapheresis, low-dose intravenous immunoglobulin (IVIG), rituximab and pre-transplant immunosuppression, AMR has been reported in more than 60% of living-donor patients with positive cytotoxic cross-match [84]. Other authors have demonstrated that positive flow cross-match [83], or higher mean flow T-cell or B-cell cross-match at time of transplant [85], increases the risk of AMR in desensitized patients compared to patients with negative or low flow cross-match.

It appears that despite desensitization, an increased risk of AMR is maintained although this is relatively low in DSA-positive patients with negative cytotoxicity and flow cross-match.

9. HLA matching

The impact of HLA mismatch on risk of acute rejection is undisputed [15,38–40,86,87]. Transplants with no mismatches have a low risk of cellular or AMR [10,15,38]. One large US registry study found that a patient receiving a kidney transplant with more than three HLA mismatches has more than a 50% increase in risk for acute rejection by year 1 versus a zero-mismatch transplant [38]. Other authors have confirmed the significant association between 4 and 6 HLA mismatches and risk for rejection [88]. HLA class II mismatch in DR loci is particularly unfavorable [10,38,40,42] (Fig. 3). The risk of AMR appears to be increased by HLA mismatching more than cellular rejection: one single-center analysis found the HRs for antibody-mediated and cellular rejection to be 5.00 and 1.86, respectively, for patients with ≥3 mismatches versus zero mismatches [15].

10. Viral serostatus matching

Data from the 1990s suggested that cytomegalovirus (CMV) mismatch was predictive for acute rejection after kidney transplantation [89], but since the adoption of CMV prophylaxis in high-risk groups no such link has been observed. One analysis of OPTN data from 24,216 transplants performed during 2004 to 2008 found no increase in the risk for acute rejection in D+/R−, D−/R+ or D+/R+ transplants compared to controls (D−/R−) [11]. Other authors have found onset of CMV infection post-transplant to have no effect on borderline or clinically-evident acute rejection [90,91].

Limited data on a possible association between Epstein–Barr infection and rejection risk, largely from pediatric transplantation, are inconclusive [92,93] and would not influence pre-transplant immunosuppression planning, although regardless of rejection risk the use of belatacept is restricted to EBV-positive recipients. Development of BK virus infection post-transplant can increase the risk of rejection due to a consequent reduction in immunosuppressive intensity, but this does not apply to the initial immunosuppression regimen, although it should be borne in mind that maintenance therapy with tacrolimus and

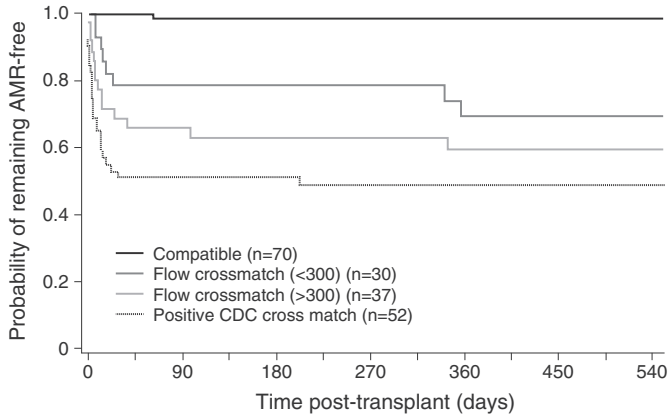

Fig. 2. Incidence of antibody-mediated rejection (AMR) in living-donor transplant patients with positive complement-dependent cytotoxicity (CDC) cross-match, high (>300) or low (<300) flow cross-match or no T-cell or B-cell cross-match at the time of transplant, following desensitization protocols tailored according to risk level [83]. Reproduced with permission.

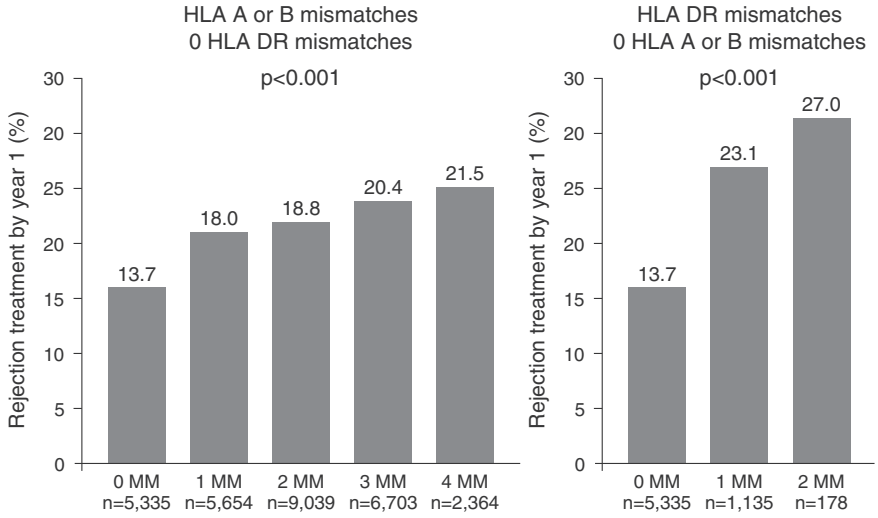

Fig. 3. Freedom from antibody-mediated rejection by year 1 post-transplant in deceased-donor kidney transplants (1990–2010) according to number of HLA A or B mismatches with 0 HLA DR mismatch, and number of HLA DR mismatches with 0 HLA A or B mismatch [10]. MM, mismatch. Reproduced with permission.

mycophenolate mofetil (MMF) may increase the risk for BK nephropathy [94–96].

11. Organ preservation

Longer cold ischemia time is a well-documented risk factor for graft loss after kidney transplantation, with every additional hour of cold ischemia increasing the risk of graft failure [97]. It has been estimated that 30 h of hypothermic preservation increases the rate of graft loss by 40% compared to six hours [97]. The impact of extended cold ischemia time arises from exacerbated ischemia–perfusion injury and greater risk of delayed graft function (DGF) [98,99], rather than through an intensified host immunological response [100], but since DGF is an established predictor for acute rejection long cold ischemia time can indirectly affect rejection risk. Large single-center analyses [41,42,101] have found small or non-significant increases in risk for acute rejection with each additional hour of hypothermic preservation when DGF was taken into account. A US registry analysis published in 2006 found a small significant effect for long cold ischemia time (>24 h versus ≤24 h: adjusted risk ratio 1.04, $p = 0.03$), but such long preservation times are now less frequent than in the past so the relevance of this is questionable [102]. For living-donor recipients, cold ischemia longer or shorter than 8 h has no effect on rejection rates [103]. In terms of assessing immunological rejection, DGF appears to be a more directly relevant risk factor than ischemic time.

It remains an open question whether the use of machine perfusion lowers the risk for rejection. An international trial compared outcomes in paired kidneys from the same donor after randomization to either machine perfusion or cold storage [104]. The primary endpoint of DGF was significantly less likely with machine perfusion (odds ratio 0.57; 95% CI 0.36–0.88; $p = 0.01$) but acute rejection by year 1 was unaffected. Another multicenter randomized trial of paired donor kidneys, this time from donors after cardiac death, again reported no difference in acute rejection by one year using either type of preservation although there was a trend to less rejection at three months with machine perfusion (7% versus 22%; $p = 0.06$) [105]. Overall, the literature does not support a clear relationship between type of preservation system and risk of rejection [104–106]. A *post-hoc* analysis of three randomized trials reported a significantly higher risk of acute rejection by one year for donor kidneys with a shorter pump time compared to paired kidneys with longer pump time (mean 22.7 h versus 31.2 h, $p < 0.001$) but this interesting finding has not been substantiated by other studies.

12. Delayed graft function

Delayed onset of graft function is generally believed to increase the risk of subsequent acute rejection [1]. A meta-analysis of 11 studies published during 1994 to 2005, which enrolled a total of 4995 patients, calculated the relative risk for acute rejection to be 1.46 (95% CI 1.29–1.47; $p < 0.001$) for patients with DGF versus no DGF, when DGF was defined as any need for dialysis [107]. A large single-center analysis in a more recent cohort (2000 to 2008) found that DGF using the more stringent definition of more than one dialysis session increased the risk for acute rejection to a greater extent (odds ratio 1.66; 95% CI 1.11–2.49; $p = 0.015$) while patients requiring only one dialysis session had no increased risk [107]. The degree to which the risk of rejection is increased in the presence of DGF suggests that modification of the planned initial regimen should be amended depending on the timing of first urine output by the graft.

13. Defining the early immunosuppression regimen

There are four main areas of decision-making when planning the initial post-transplant regimen: (i) the possible use of pre-transplant desensitization strategies [81] (ii) the use and type of induction therapy [108] (iii) initiation of standard versus minimized CNI exposure from time of transplant [109] and (iv) whether steroid avoidance (<7 days administration) should be attempted [110]. A detailed discussion of these early options – and longer-term immunosuppression regimens based on the post-transplant course – is beyond the scope of this article. Key points, however, are summarized in Table 1. As an example, a patient with preformed DSA receiving a second transplant is likely to be a candidate for desensitization strategies while, at the other end of the risk spectrum, a non-sensitized patient without positive indicators of humoral sensitization may not benefit from induction therapy [24], or could be suitable for a steroid-avoidance regimen. A further point to consider is the likely adherence of the patient to the prescribing regimen. As discussed above, non-adherence is highly predictive for rejection and graft loss, and where the risk of non-adherence appears high aggressive CNI or steroid minimization strategies (or complex dosing regimens) may be inadvisable.

14. Conclusion

The opportunities to tailor choice of induction therapy and the initial maintenance immunosuppression after kidney transplantation have

never been greater, requiring a more refined pre-transplant assessment of immunological risk than in the past. Transplant clinicians are faced with a myriad of factors to consider, and although robust individualized risk assessment is not yet feasible, patients can be stratified into different immunological risk groups (Table 2). Some characteristics – such as deceased donation and duration of cold ischemia time – have become less important over time. Others confer only a minor increase in risk or, indeed, have not consistently shown an effect, such as recipient gender or presence of soluble CD30. A few conventional risk factors remain critical and should always be taken into account, notably the presence of HLA antibodies independent of DSA, and HLA mismatch (particularly HLA DR and DQ mismatch). Increasingly, however, there is a shift towards decision-making based on newer, more subtle pre-transplant immunology tests. PRA monitoring has been superseded by more subtle single-bead assays to detect the types of preformed HLA antibodies. Non-HLA antibodies such as AT1R-Abs or ELISPOT testing are likely to further refine laboratory-based assessment of risk.

Algorithms which take into account the complexity of immune factors, together with pharmacogenetics and donor factors, could become more relevant in the future and follow trends in other areas of precision medicine [111].

Table 2
Overview of pre-transplant risk factors for acute rejection after kidney transplantation.

Risk factor	Importance	Comment
Recipient age		
Younger age	++	Stronger immune response
Adolescence	+++	Higher risk for non-adherence
Donor age	+	Trend towards higher immunogenicity in older organs
Recipient gender	+	Trend to fewer rejections in males
Ethnicity	+++	Significantly higher risk of rejection in African Americans
Deceased vs living donor	+	Diminishing differences (also little difference between deceased donation after cardiac vs brain death, or expanded versus criteria donation)
Previous transfusion	+	Considered 'low immunologic responder' if patient is unsensitized despite previous transfusion
Previous transplantation	++[a]	No relevant increase in risk if the patient remains unsensitized despite prior transplantation. Early loss of previous graft to immunological causes increases risk of rejection after next graft
Previous pregnancy	++	Increasing risk with successive pregnancies
PRA >0% (HLA antibodies)	+++	Applies to both historic and current PRA level, HLA antibodies Class I and/or Class II
Preformed HLA DSA (>500 MFI)	++++	Having no preformed HLA DSA at transplant is associated with low immunological risk; low levels of non-cytotoxic HLA antibodies confer intermediate risk. De novo HLA DSA post-transplant monitoring is required
AT1 receptor antibodies	++	Test is relatively widely available
T-cell ELISPOT	++	Time-consuming (1–2 days) and requires large blood volume; may be more relevant for living-donor transplants
Soluble CD30	+	Inconclusive data
Sensitized patients after desensitization	++/+++	Increased risk of AMR appears to be sustained after desensitization in DSA-positive patients with negative cytotoxicity and flow cross-match, but to a far lesser extent than in patients with positive cytotoxic (profound increase in risk) or flow cross-match (moderate increase in risk)
HLA mismatch	+++	Marked and well-documented effect on cellular and antibody-mediated rejection. Particularly pronounced for HLA DR mismatch
CMV mismatch	–	No association between CMV mismatch and acute rejection in the era of CMV prophylaxis
EBV mismatch	–	No effect *per se* on acute rejection
Cold ischemia time	+	Less important with current shorter ischemic times
Machine preservation	+	Minor effect versus cold storage; not well-documented
Delayed graft function	+++	Delayed function may prompt changes to the planned protocol in the first few days post-transplant

CMV, cytomegalovirus; DSA, donor specific antibodies; EBV, Epstein Barr virus; HLA, human leukocyte antigen; MFI, mean fluorescence intensity; PRA, panel reactive antibodies.
– Negligible or undocumented effect.
+ Mild effect or weak evidence.
++ Moderate effect with acceptable evidence.
+++ Strong, well-documented effect.
[a] Only if the patient is sensitized.

Conflict of Interest

Johann Pratschke is a member of Advisory Boards for Sanofi and Novartis, and has received speaker's honoraria from Sanofi, Novartis, Astellas, Chiesi and Teva. Duska Dragun is a member of Advisory Boards for Sanofi and Novartis, and has received speaker's honoraria from Sanofi, Novartis, Astellas, Pfizer and Hexal. Ingeborg A. Hauser has served as an Advisory Board Member for Chiesi, Novartis, Sanofi and Teva, and has received travel grants and/or speaker's honoraria from Astellas, Hexal, Novartis, Roche and Sanofi. Sabine Horn is a member of Advisory Boards for Sanofi and Otsuka, and has received both travel grants and speaker´s honoraria from Novartis, Sandoz, Fresenius, Amgen, Menarini and Astellas. Thomas F. Mueller is a member of a Sanofi Advisory Board and has received travel grant from Astellas. Peter Schemmer served over the last five years as an Advisory Board Member for Astellas, Baxter, Biotest, Chiesi, Novartis, Sanofi, Teva and received both travel grants and speaker honorarium by from Astellas, Bayer, Biotest, Covidien, Dr. Köhler Chemie, Falk Foundation e.V., Hexal, Novartis, Panacea Biotec and Sanofi. Friedrich Thaiss is an advisory board member for: Sanofi and Novartis, has taken part in clinical trials for Novartis, Alexion, BMS and Shire, and has received educational grants from Sanofi, Novartis, Astellas, Pfizer and Hexal.

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